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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/069,541	02/27/2002	Tatsuya Haga	31671-176438	1435

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EXAMINER	
NICHOLS, CHRISTOPHER J	

ART UNIT	PAPER NUMBER
1647	

DATE MAILED: 05/26/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/069,541	HAGA ET AL.	
	Examiner	Art Unit	
	Christopher J Nichols, Ph.D.	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 March 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *2-7,11-13,15-18,21-25,27-33,35,36,38-63,66 and 68-112* is/are pending in the application.

4a) Of the above claim(s) *See Continuation Sheet* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *99-112* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *2-7,11-13,15-18,21-25,27-33,35,36,38-63,66 and 68-112* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *27 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Continuation of Disposition of Claims: Claims withdrawn from consideration are 2-7,11-13,15-18,21-25,27-33,35,36,38-63,66 and 68-98.

DETAILED ACTION

Status of Application, Amendments, and/or Claims

1. The Response and Amendments filed 8 October 2003 and 16 March 2004 have been received and entered in full.

2. The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Withdrawn Objections And/Or Rejections

3. All Objections and Rejections of claims **1, 8, 9, 10, 14, 19, 20, 26, 34, 37, 64, 65,** and **67** as set forth in the previous Office Action (8 July 2003) are *moot* in view of Applicant's cancellation of said claims (8 October 2003 and 16 March 2004).

New Objections And/Or Rejections

Claim Objections

4. Claims **100, 103,** and **107** are objected to because of the following informalities: the claims do not end in a period. Appropriate correction is required.

5. Claim **110** is objected to because of the following informalities: chromosome is misspelled. Appropriate correction is required.

6. Claims **107** and **109** are objected to under 37 CFR 1.75(c) as being in improper form because a multiple dependent claim must refer to the parent claims in the alternative only. See MPEP § 608.01(n).

Claim Rejections - 35 USC § 112

7. Claims **99-109** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an isolated gene comprising an amino acid sequence represented by SEQ ID NO: 6 or an isolated host cell transfected with same and a protein or fusion protein comprising SEQ ID NO: 6*, does not reasonably provide enablement for *a protein comprising an amino acid sequence where one or a few amino acids are deficient, substituted, or added in the amino acid sequence represented by SEQ ID NO: 6 or a protein comprising an amino acid sequence where one or a few amino acids are deficient, substituted, or added in the amino acid sequence represented by SEQ ID NO: 6.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

8. The claims are drawn very broadly to any given isolated human-derived gene expressed in a cholingeric neuron, a protein comprising an amino acid sequence represented by SEQ ID NO: 6, and any of the aforementioned with mutations. The claims also encompass any nucleic acids which encode a high affinity choline transporter activity, any nucleic acids which hybridize to it, and any fusion proteins made using the aforementioned nucleic acids. The language of said claims encompasses known as well as unknown genes and proteins which encode or are protein which show high affinity choline transporter activity.

9. The specification teaches that the polynucleotide of SEQ ID NO: 5 encodes the protein of the amino acid sequence of SEQ ID NO: 6 which is a human high affinity choline transporter.

10. The specification fails to provide any guidance for the successful cloning, isolation, and characterization of variants, fragments, polymorphisms, isoforms, and analogues of the amino

acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity. And since resolution of the various complications in regards to targeting the role a particular amino acid in a protein is highly unpredictable, one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation. In order to practice the invention using the specification and the state of the art as outlined below, the quantity of experimentation required to practice the invention as claimed would require the *de novo* determination of the variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed.

11. Additionally, a person skilled in the art would recognize that predicting the efficacy of making or using variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity based solely on suggestion is highly problematic (see MPEP §2164.02). Thus, although the specification prophetically considers and discloses general methodologies of making and using variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity, such a disclosure would not be considered enabling since the state of protein biochemistry is highly unpredictable. The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;

(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

12. The following references are cited herein to illustrate the state of the art of protein biochemistry.

13. Regarding derivatives and fragments of the polypeptides of the amino acid sequence of SEQ ID NO: 6, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 433-506]. However, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein

which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of

working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

14. Applicant traversed the rejection of the previously presented claims in the Response filed (8 October 2004 and 16 March 2004). The relevant grounds of Applicant's arguments are responded to herein: **(a)** claims not limited to or directed to a sequence represented by a SEQ ID NO can not be rejected as limited in scope to one, **(b)** a skilled artisan can arbitrarily use an amino acid sequence where one or a few amino acids are changed, **(c)** failure to obtain a patent as desired by Applicant may have deleterious repercussions, and **(d)** the rejection is not in compliance with the Examination Standard of the Japanese Patent Office.

15. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

16. On "**(a)**", as instantly presented the generic claims 99 and 104 encompass the specific embodiment of the amino acid sequence of SEQ ID NO: 6. Thus a scope of enablement rejection establishes that one or more aspects of a broader claim are enabled, such in the instant case where a high-affinity choline transporter protein comprising the amino acid sequence of SEQ ID NO: 6 encoded by the nucleotide sequence of SEQ ID NO: 5 is enabled but not broader non-enabled embodiments of the claims.

17. On "**(b)**", while the cloning, isolation, and characterization of variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that

retains the desired high-affinity choline transporter activity may constitute a fecund ground for investigation, the CAFC ruled in *Genentech Inc. v. Novo Nordisk A/S* (CA FC) **42 USPQ2d 1001** (1997) that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Citing *Brenner v. Manson,* **383 U.S. 519, 536, 148 USPQ 689, 696** (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Therefore the CFAC stated that tossing out the mere germ of an idea does not constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. That requirement has not been met in the instant specification with respect to the any variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 (or nucleic acids which may encode said polypeptides) that retains the desired high-affinity choline transporter activity.

18. On "**(c)**", decisions concerning whether or not a patent is "worth it" emotionally or financially is not the purview of the Examiner.

19. On "**(d)**", the Examination Standard of the Japanese Patent Office is not relevant to the instant examination. Examination of all US and National Stage patent applications are done in accordance to United States law.

20. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *prophetic suggestion* as exemplified in the references herein.

21. Claims **110-112** are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *an in vitro method of preparing a cell having high-affinity choline transport activity comprising introducing DNA encoding SEQ ID NO: 5 into said cell and the isolated cell made by said in vitro method,* does not reasonably provide enablement for *the practicing of said method in vivo (gene therapy) or transgenic animals made by the claimed method.* The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make or use the invention commensurate in scope with these claims.

22. The above invention is drawn to methods of transfecting a cell with a DNA encoding a protein with high-affinity choline transporter activity. The language of said claims encompasses both *in vivo* and *in vitro* transfection (transfection, transformation, and gene therapy).

23. The specification teaches that the nucleotide sequence of SEQ ID NO: 5 encodes an amino acid sequence of SEQ ID NO: 6 which is a protein with high-affinity choline transporter activity. The nucleotide sequence of SEQ ID NO: 5 has been successfully introduced into oocytes and COS7 cells *in vitro* and express an amino acid sequence of SEQ ID NO: 6 which is a protein with high-affinity choline transporter activity. But the claims are drawn very broadly to methods of introducing DNA encoding a protein with high-affinity choline transporter activity into cell lines and patients (i.e. gene therapy). Since the specification fails to provide any guidance for the successful introduction of a DNA encoding a protein with high-affinity choline transporter activity into a patient (whether human or animal) and since resolution of the various complications in regards to targeting a particular gene in an organism is highly unpredictable,

one of skill in the art would have been unable to practice the invention without engaging in undue trial and error experimentation.

24. The specification as filed does not provide any guidance or examples that would enable a skilled artisan to use the disclosed methods of introducing a DNA encoding a protein with high-affinity choline transporter activity into an animal. Additionally, a person skilled in the art would recognize that predicting the efficacy of using a specific DNA encoding a protein with high-affinity choline transporter activity *in vivo* based solely on its performance *in vitro* is highly problematic. Thus, although the specification prophetically considers and discloses general methodologies of using the claimed methods in *in vivo* gene therapy or to make transgenic animals, such a disclosure would not be considered enabling since the state of gene therapy is highly unpredictable [see Verma and Somia (18 September 1997) "Gene therapy- promises, problems, and prospects." Nature **389**: 239-241; Eck and Wilson (1996) Chapter 5: "Gene-Based Therapy" **Goodman & Gilmans's The Pharmacological Basis of Therapeutics 9th Ed.** (pp. 77-100)] The factors listed below have been considered in the analysis of enablement [see MPEP §2164.01(a) and *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988)]:

(A) The breadth of the claims;
(B) The nature of the invention;
(C) The state of the prior art;
(D) The level of one of ordinary skill;
(E) The level of predictability in the art;
(F) The amount of direction provided by the inventor;
(G) The existence of working examples; and
(H) The quantity of experimentation needed to make or use the invention based on the content of the disclosure.

25. The following references are cited herein to illustrate the state of the art of a gene therapy.

26. On the breadth of the claims, gene therapy is a notoriously difficult undertaking. The major barrier to overcome is that of the appropriate gene therapy vector (the vehicle by which the gene or DNA is introduced). Jane *et al.* (October 1998) "Vector development: a major obstacle in human gene therapy." Ann Med. **30**(5): 413-5 teaches that gene therapy has been proposed for a wide variety of human conditions including monogenic disorders, such as the haemoglobinopathies and immunodeficiency syndromes, cancer and many other diseases. Prerequisites for the success of this approach include the ability to deliver the therapeutic gene intact to the target cell, persistent levels of transgene expression sufficient to correct the disease phenotype, lack of unwanted side-effects associated with vector exposure or gene transfer and relative simplicity allowing the widespread use of this methodology. Although substantial progress has been made in animal models since the inception of genetic therapy in the early 1980s, significant obstacles remain for human therapy, most notably in the area of vector development. The first generation of gene therapy vectors has failed to overcome many of the biological hurdles cited above necessitating the development of alternate means of gene delivery and expression. No guidance or examples are present in the instant Specification as to show the skilled artisan that these obstacles have been addressed.

27. On the nature of the invention, while *in vitro* introduction of DNA (genes) into cells (transfection or transformation) is commonplace, the practice of *in vivo* introduction of DNA (genes) is fraught with complications. For instance, Potter & Chang (18 June 1999) "Review—The use of immunosuppressive agents to prevent neutralizing antibodies against a transgene product." Ann N Y Acad Sci. **875**: 159-74 teaches that a major obstacle to successful gene therapy is the *in vivo* production of neutralizing antibodies against the recombinant therapeutic

product delivered (Table 2). This is a problem inherent to all gene therapy methods, regardless of the vector used to deliver the protein (Figure 2). The Specification as filed does not address how these complications with may negate the effect of the foreign gene may be overcome. Further the claims require the target to lack the high-affinity choline transporter therefore it has a greater chance of being recognized as being "foreign" and thus immunologically cleared preventing its uptake and incorporation.

28. On the state of the prior art, gene therapy is a complicated undertaking for which a fair amount of guidance is necessary beyond suggestion. An analogous attempt to the one claimed is described by Rozmahel *et al.* (July 1997) "Incomplete rescue of cystic fibrosis transmembrane conductance regulator deficient mice by the human CFTR cDNA." Hum Mol Genet. 6(7): 1153-62 teaches a mouse model used to study the ability of human CFTR to correct the defect in mice deficient of the endogenous protein. In this model, expression of the endogenous Cftr gene was disrupted and replaced with a human CFTR cDNA by a gene targeted 'knock-in' event (Figure 1). Animals homozygous for the gene replacement failed to show neither improved intestinal pathology nor survival when compared to mice completely lacking CFTR (Figure 3 & 4). RNA analyses showed that the human CFTR sequence was transcribed from the targeted allele in the respiratory and intestinal epithelial cells. Furthermore, *in vivo* potential difference measurements showed that basal CFTR chloride channel activity was present in the apical membranes of both nasal and rectal epithelial cells in all homozygous knock-in animals examined. Ussing chamber studies showed, however, that the cAMP-mediated chloride channel function was impaired in the intestinal tract among the majority of homozygous knock-in animals. Hence, failure to correct the intestinal pathology associated with loss of endogenous CFTR was related to inefficient

functional expression of the human protein in mice. Therefore although the instant Specification describes a functional high-affinity choline transporter gene this may not be necessary and sufficient to accomplish the goal of gene therapy especially complete replacement of a missing gene. Therefore the claims as instantly presented constitute an invitation to experiment in the absence of sufficient guidance.

29. Regarding derivatives and fragments of the nucleotide sequence of SEQ ID NO: 5, the problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. These or other regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. In this regard, Applicant has provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change (e.g. such as by amino acid substitutions or deletions), and the nature and extent of

changes that can be made in these positions. Although the specification outlines art-recognized procedures for producing and screening for active muteins, this is not adequate guidance as to the nature of active derivatives that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, they may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39, especially p. 36 at Box 2; Doerks *et al.*, (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427]. Due to the large quantity of experimentation necessary to generate the infinite number of derivatives recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the

unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

30. Applicant traversed the rejection of the previously presented claims in the Response filed (8 October 2004 and 16 March 2004). The relevant grounds of Applicant's arguments are responded to herein: the cloning, isolation, and characterization of variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity and the use thereof in gene therapy or to make transgenic animals is possible.

31. Applicant's arguments have been taken into consideration and are not found persuasive for the following reasons.

32. While the cloning, isolation, and characterization of variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity and the use thereof in gene therapy or to make transgenic animals may constitute a fecund ground for investigation, the CAFC ruled in *Genentech Inc. v. Novo Nordisk A/S* (CA FC) **42 USPQ2d 1001** (1997) that patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Citing *Brenner v. Manson,* **383 U.S. 519, 536, 148 USPQ 689, 696** (1966) (stating, in context of the utility requirement, that "a patent is not a hunting license. It is not a reward for the search, but compensation for its successful conclusion."). Therefore the CFAC stated that tossing out the mere germ of an idea does not

constitute enabling disclosure. While every aspect of a generic claim certainly need not have been carried out by an inventor, or exemplified in the specification, reasonable detail must be provided in order to enable members of the public to understand and carry out the invention. That requirement has not been met in the instant specification with respect to the any variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity and the use thereof in gene therapy or to make transgenic animals.

33. In order to practice the invention using the specification and the state of the prior art as outlined above, the quantity of experimentation required to practice the invention as claimed *in vivo* would require the *de novo* determination of conditions for successful incorporation of a DNA encoding a protein with high-affinity choline transporter activity into the genome of an animal. In the absence of any guidance from the specification, the amount of experimentation would be undue, and one would have been unable to practice the invention over the scope claimed. Thus the specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *in vitro* experiments to the *in vivo* transfection of a gene encoding a protein having high-affinity choline transporter activity as exemplified in the references above.

34. Claims **99, 101-104,** and **106-109** are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

35. The claims are drawn to gene encoding polypeptides and polypeptides having high-affinity choline transporter activity.

36. The claims are drawn to a substantially purified and human derived DNA encoding a protein that hybridizes to a particular sequence.

37. The claims are also drawn to a recombinant protein expressed in a cholinergic neuron a having the activity of high-affinity choline transporter.

38. The claims are further drawn to an isolated protein with as of yet unspecified mutations.

39. The claims do not require that the polypeptide possess any particular conserved structure. Thus, the claims are drawn to a genus of polypeptides and polynucleotides that are defined by a broad activity, general cell origin, and desired hybridization.

40. To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, and any combination thereof. In this case, the only factor present in the claim that is sufficiently disclosed is a relatively defined function. The specification does not identify any particular portion of the structure that must be conserved, nor does it provide a disclosure of structure/function correlation. The distinguishing characteristics of the claimed genus are not described. The only adequately described species is a polypeptide comprising SEQ ID NO: 6. No active variants are disclosed. Accordingly, the specification does not provide adequate written description of the claimed genus.

41. *Vas-Cath Inc. v. Mahurkar*, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See *Vas-Cath* at page 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016.

42. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In *Fiddes*, claims directed to mammalian FGF's were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

43. Applicant traversed the rejection of the previously presented claims in the Response filed (8 October 2004 and 16 March 2004). Applicant's arguments have been taken into consideration and are not found persuasive because Applicant has failed to evidence material possession of the invention as claimed. MPEP §2145 clearly states that attorney argument is not evidence unless it is an admission, in which case, an examiner may use the admission in making a rejection (MPEP § 2129 and §2144.03).

44. Furthermore, the arguments of counsel cannot take the place of evidence in the record. In the instant case the Applicant is asserting that the Specification teaches variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity while no data, information, or teaching supports variants, fragments, polymorphisms, isoforms, and analogues of the amino acid sequence of SEQ ID NO: 6 that retains the desired high-affinity choline transporter activity in the instant Specification {see *In re Schulze*, 346 F.2d 600, 602, 145 USPQ 716, 718 (CCPA 1965); *In re Geisler*, 116 F.3d 1465, 43 USPQ2d 1362 (Fed. Cir. 1997) ("An assertion of what seems to follow from common experience is just attorney argument and not the kind of factual evidence that is required to rebut a prima facie case of obviousness.") and MPEP § 716.01(c)}.

45. Therefore, only isolated polypeptides comprising the amino acid sequence set forth in SEQ ID NO: 6, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision.

46. Claim **103** is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "stringency" in claim 10 is a relative term which renders the claim indefinite. The term "stringency" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention.

47. Applicant traversed the rejection of the previously presented claims in the Response filed (8 October 2004 and 16 March 2004). The relevant grounds of Applicant's arguments are responded to herein.

48. The specification of the instant application fails to provide adequate guidance for one of skill in the art to overcome the unpredictability and challenges of applying results from *prophetic suggestion* as exemplified in the references herein.

49. To satisfy the requirements of 35 U.S.C. §112 ¶2 Applicant must unambiguously define the limitations of the claims. "Stringent conditions" for hybridization, while known the art, are not unambiguously defined. A great deal of latitude and a range of conditions may be construed as "stringent". Also, stringency may be low, moderate, or high, none of which is specified by the claims as instantly neither presented nor supported by the Specification. For instance, the Roche website defines hybridization conditions under four parameters: temperature, pH, concentration of monovalent cations, and the presence of organic solvents, none of which are defined by the claims or the Specification ("Nucleic Acid Hybridization- General Aspects" pp. 33-37 Roche website retrieved on 12 May 2004). Also the NIH Division of Intramural Research teaches that "Nucleic Acid Hybridization" conditions vary. For temperature it teaches that it may be 25oC below duplex melting temperature, which varies due to the length of the polynucleotide and the GC content. Also, salt concentrations may vary between 5 to 6x SCC and denaturing agents such a formamide ranges from 1% to 50% (NIH Division of Intramural Research "Nucleic Acid Hybridization" retrieved from NIH website on 12 May 2004). Therefore the skilled artisan is not apprised of the metes and bounds of what constitutes "stringent conditions". Neither the

specification nor the art defines the term unambiguously. Thus the metes and bounds of the claims cannot be determined.

50. Claims **99, 104,** and **108** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

51. Claim 99 recites the limitation of "An isolated human-derived gene expressed in a cholingergic neuron". It is not clear from the construction of the claim as where the invention lies, in the "isolated human-derived gene" or the "cholingergic neuron".

52. Claim 104 recites the limitation of "A human-derived recombinant protein expressed in a cholingergic neuron". It is not clear from the construction of the claim as where the invention lies, in the "human-derived recombinant protein" or the "cholingergic neuron".

53. Claim 108 recites the limitation of "...an expression system which can express a human-derived protein expressed in a cholingergic neuron". It is not clear from the construction of the claim as where the invention lies, in the "expression system", "human-derived protein", or the "cholingergic neuron".

54. The language of the claims fails to clearly and distinctly set forth what the Applicant considers to be their invention.

55. Claims **110-111** are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

56. The method claims have confusing and unclear language. It is not clear from the construction of the claims as where the invention lies. The claims do not clearly state whether the method lies in transforming/transfecting cells, gene therapy, or recombinant expression for purification.

57. Claims **110-111** are rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: how the gene or DNA is introduced.

Summary

58. No Claims are allowed.

59. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

60. A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Christopher James Nichols, Ph.D.** whose telephone number is **(571) 272-0889**. The examiner can normally be reached on Monday through Friday, 8:00 AM to 6:00 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, **Gary Kunz, Ph.D.** can be reached on **(571) 272-0887**.

The fax number for the organization where this application or proceeding is assigned is **703-872-9306**.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see **http://pair-direct.uspto.gov**. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at **866-217-9197** (toll-free).

Elizabeth C. Kemmerer

CJN
May 20, 2004

ELIZABETH KEMMERER
PRIMARY EXAMINER